THE USE OF HYPOTHERMIA IN CARDIAC SURGERY*

HENRY SWAN

Because hypothermia slows the metabolic processes of the body, oxygen consumption and circulatory energy are reduced. This modality, therefore, suggested itself as being of potential value in the operative therapy of heart disease. Indeed, the possibility of this technique as a method for open intra-cardiac operation under direct vision during total circulatory occlusion was the stimulus which, for the past three years, has directed our experimental and clinical attention toward attempting to elucidate some of the alterations in physiology occurring in cooled and rewarmed individuals, and toward the elaboration of intracardiac operative techniques which could be safely performed by this method.

This report is concerned with an analysis of 24 patients who underwent standard closed cardiac operations, and 31 patients who underwent 84 open-heart operative procedures during hypothermia.

Preparation of patients for hypothermic anesthesia is essentially similar to any anesthetic procedure. Morphine, Demerol, barbiturates, and scopolamine are given for pre-medication. Induction is usually with ether. Two intravenous cannulae are placed to assure that this route for fluids or blood will be available. Electrocardiograph needle electrodes are connected and a rectal thermocouple inserted. Throughout the induction and cooling period a surgeon is available for immediate cardiac resuscitation if need arises. This precaution was instrumental in saving at least two patients who underwent circulatory arrest before thoracotomy had been performed.

When the patient is in second plane, third stage anesthesia he is placed in a tub of tepid water. The head and arms are held up out of the water. If shivering ensues, d-tubocurarine is given. When vital signs are stable, ice cubes are added to the water. Hyperventilation is deliberately performed throughout the anesthetic experience, except during circulatory occlusion.

The patient is removed from the tub when the rectal temperature has reached a point which is about two-thirds the desired fall. This figure varies somewhat, but the end temperature can be estimated in this fashion, usually, within a margin of error of one or one and a half degrees centigrade. To cool an infant requires about 10–15 minutes in the tub, while an obese adult may need as long as an hour or an hour and 15 minutes.

When the patient is removed from the tub, he is thoroughly dried. The pelvic area is wrapped with one-inch felt which is taped in place. A standard diathermy coil is then accurately placed, taking care that the patient is supported so his weight does not lie on the coils. The diathermy is used to counteract a tendency to overdrift in cooling, and to warm the patient immediately following completion of the cardiac procedure. Blood replacement is begun early and attempt is made to keep pace with the rate of loss. Indeed, transfusion slightly in excess of loss is considered desirable.

About one-half of the patients show auricular fibrillation when rectal temperatures

* This study was aided in part by a grant from the United States Public Health Service (H-1559 C), and in part by a grant from the American Heart Association.

are in the high twenties (C.). We do not consider this a serious development, and most will revert to sinus rhythm at about the same temperature when rewarming.

About five minutes before the moment of circulatory occlusion, further curare is given to prevent contraction of the diaphragm. A determination of blood pH is made at this time. We believe it desirable that the patient be in a state of respiratory alkalosis, with a pH of 7.5 or greater. During occlusion the lungs are allowed to collapse completely, and respiration is discontinued. The surgeon occludes the inflow of blood to the heart; then, after a few seconds, occludes the aorta about one inch distal to the valve and injects 0.8–1.5 cc. neostigmine 1:4000 into the base of the aorta so that it will perfuse the coronary system. After an additional 10 or 15 seconds, the operative manipulation is performed.

Upon release of circulatory occlusion, the lungs are again ventilated with oxygen, and hyperventilation resumed. The patient may receive only oxygen until the end of the procedure. If further anesthetic agent is needed it usually consists of 50–50 nitrous oxide-oxygen.

Diathermy is now begun, applied intermittently—one minute off, two on—to help prevent skin burns. Attempt is made to have the patient have an auscultable blood pressure of 90 systolic or above before the thoracotomy is finally closed, in order to avoid later bleeding when the hypotension of hypothermia rises to normal levels. Upon completion of closure, the patient may or may not be further warmed in the tub filled with water at 45° C., depending on temperature. The endotracheal tube is removed when spontaneous respirations appear adequate. The usual temperature of waking is about 34° C.

The immediate postoperative period is extremely critical. Evaluation of effective circulating blood volume and myocardial function is extraordinarily difficult. A few cases of severe shock occurred at this time. Blood volume studies are done at this time to compare with preoperative levels. Improved understanding of the state of the circulation immediately following cooling is badly needed in order to control this stage of hypothermia more intelligently.

In the management of hypothermia, we have emphasized the following safety measures on the basis of personal experimental and clinical experience. We believe that a sudden shift of blood pH from respiratory acidosis toward normal may incite onset of ventricular fibrillation and that a high pCO_2 sets the stage for the induction of cardiac arrest. For this reason, we deliberately strive for a respiratory alkalosis throughout the procedure.

We use neostigmine for the coronary perfusion on the basis of experimental data suggesting its value. Concomitant with its clinical use, the incidence of ventricular fibrillation fell markedly. In fact, we have had no patient undergo this complication in the last thirty cases.

The prevention of coronary air embolus is highly important. To this end, we make it a practice to occlude the ostia of the coronary arteries with a non-crushing clamp during the open portion of the procedure, and to evacuate air by flooding the heart with Ringer's solution before circulation is resumed. Clamping the coronary arteries removes all coronary blood flow throughout the occlusion period and, therefore, is probably undesirable from this point of view. The maneuver probably shortens the safe duration of occlusion. However, the risk of coronary embolism

is so great that, in our hands, it is one of the serious limiting factors relating to open-heart techniques. In order to fill the heart with the Ringer's solution, the incision in the heart must be positioned *at the uppermost portion of the heart.* This requires wide exposure and demands a bilateral thoracotomy with a sternum-splitting incision. It also limits the cardiotomy in our hands to a right-sided incision; we have not been able to devise a safe left-heart approach which places the incision uppermost. This technique has been effective in our hands to the extent that coronary air embolus has occurred only twice in this series. Both patients were resuscitated by pumping and massaging the air through to the venous side of the coronary circulation.

Cardiac resuscitation has been done in standard fashion using intermittent manual compression, electric shock, potassium chloride, calcium chloride, and adrenalin as appeared indicated. The diathermy is an important adjunct in warming the patient when attempting to revert ventricular fibrillation.

No preoperative drugs have been used to affect cardiac action, except that digitalis was given to patients in frank failure. Pre- and postoperative penicillin is routinely used.

INDICATIONS

In congenital or acquired heart disease for which standard closed operative techniques are planned, the indications for hypothermia have been the following. In cyanotic heart disease, it was thought that the reduction in oxygen demand would result in better oxygenation of the tissues. A blue child gradually becomes pinker as temperature falls. We consider operative risk to be improved under these conditions. In heart disease associated with severe tachycardia, the extremely rapid rate we consider *per se* as undesirable. A patient with so-called atypical patent ductus, with a large heart pounding at 170, changes to one whose heart is quietly beating at 90. We are not sure, because we have not had sufficient experience, whether heart failure may not also be an additional indication.

On the other hand, patients with valvular disease resulting in left ventricular hypertrophy and strain appear to tolerate hypothermia less well. Our experience with this group is very small as yet, and we have only very preliminary impressions. It may develop that for some cardiac patients hypothermia improves risk; for others it does not.

The main indication for hypothermia in this series, however, has been its use to allow total circulatory arrest in order to perform direct-vision intra-cardiac operations. Selection of patients was largely limited to congenital diseases for which pre-existing operative techniques had proven to yield poor or inconsistent results, for example, isolated pulmonary valvular stenosis, or those for which standardized methods had not yet been developed, for example, septal defects.

COMPLICATIONS

Postoperative evaluation of the state of the circulation for several hours post-hypothermia is extremely difficult. During this period, we lost four patients due to hemorrhage, which was unrecognized and therefore untreated. For this reason, warming with diathermy until blood pressure is obtainable before closing the chest

is now routine. In addition, if there is evidence of postoperative bleeding, re-exploration will, in the future, be more promptly done.

Postoperative thrombo-embolism was the cause of death in three patients, all adults with repair of large atrial septal defects. We feel that the very large pulmonary vascular tree associated with this disease may allow stagnation and intravascular clotting when the blood flow through the lungs is drastically reduced by repair of the lesion. For this reason, in such patients we are now giving postoperative anticoagulants in an effort to forestall this complication.

Cardiac arrhythmias, especially ventricular fibrillation, occurred with considerable frequency in the early part of our series. Even though these hearts were usually restored to a regular rhythm by resuscitative measures, the patients often died in the postoperative period. Reducing the parameters of circulatory occlusion has been one factor, we believe, in reducing the risk of this complication.

In figure 1 is seen the relationship of the degree of hypothermia to mortality rate. As can be seen, patients whose temperatures are lowered below 26° C. have a sharp rise in their risk.

In figure 2 is seen the relationship between the duration of total circulatory occlusion and mortality rate. It is clear that maintaining circulatory arrest beyond eight minutes also causes a marked rise in risk.

It might be argued that the patients who were cooled below 25° C. were those with the biggest, sickest hearts. We needed more time and, for this reason, sought deeper hypothermia. Be that as it may, the fact remains that we did not achieve a safe prolonged operative time in these patients by this means.

For these reasons, we have come to believe that the safe parameters of open-heart surgery under hypothermia as we now employ it are procedures which can be done through a right cardiotomy, in less than eight minutes of occlusion time, at temperatures above 26° C.

Except for one patient with cerebral embolus, no brain damage was experienced by any patient in this series. The degree of cooling appears adequate to protect the

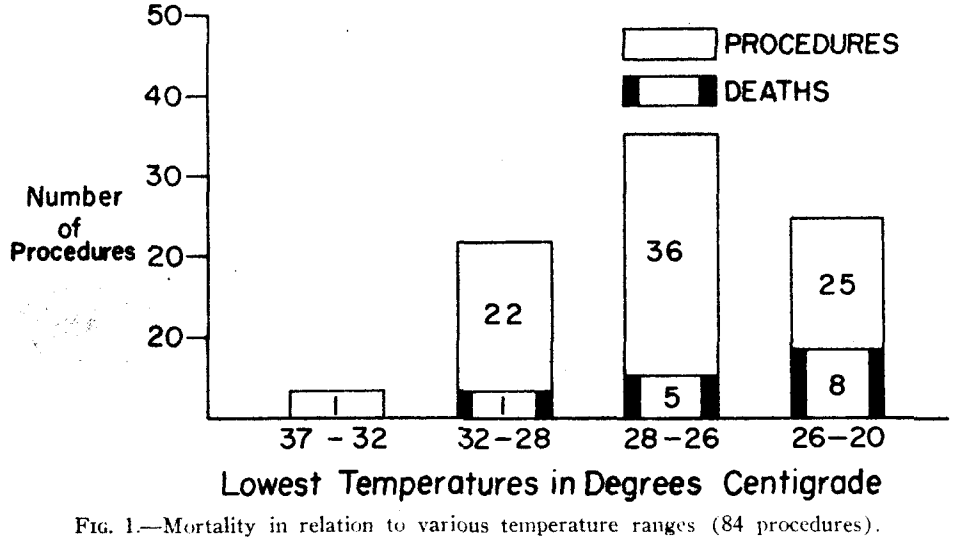

FIG. 1.—Mortality in relation to various temperature ranges (84 procedures).

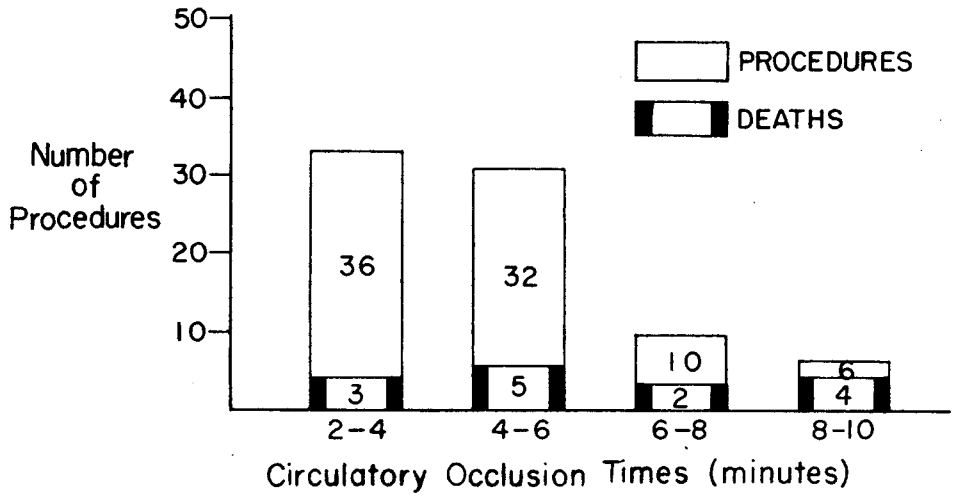

FIG. 2.—Mortality in relation to duration of circulatory occlusion (84 procedures).

higher centers for the periods of circulatory occlusion practised. A peripheral neuropathy, however, did frequently occur. This was carefully evaluated by our neurology service and the conclusion was reached that it was a complication of our method of surface cooling. The lesion was a direct injury to the peripheral nerves of the extremities due to cold. Time is an important factor. Few lesions appeared when the patient remained in ice water less than thirty minutes. For this reason, we now make it a practice to elevate the extremities above the water level after that period of time. Fortunately, all of the patients have experienced a return to normal function during the postoperative period.

CLINICAL EXPERIENCE AND RESULTS

In table I is seen the various diagnoses for which hypothermia was used in conjunction with standard closed operative procedures. In such small groups, the

TABLE I

CLOSED CARDIAC PROCEDURES

Diagnosis	Patients	Improved or cured	Unimproved	Died
Tricuspid atresia	3	0	1	2
Tetralogy of Fallot	2	2	0	0
Single ventricle	1	0	0	1
Idiopathic pulmonary hypertension	1	0	0	1
Patent ductus arteriosus	6	6	0	0
Aberrant pulmonary veins	2	1	0	1
Aorto-pulmonary window	1	1	0	0
Auricular septal defect	1	0	1	0
Aortic stenosis	1	0	1	0
Aortic regurgitation	2	0	0	2
Mitral stenosis and regurgitation	4	1	3	0
	24	11	6	7

mortality figures are without significance. However, we were impressed with its apparent beneficial effect on the operative course of cyanotic children and in patients with patent ductus arteriosus and pulmonary hypertension.

In table II is seen our experience with 81 patients who had 84 open-heart operations with total circulatory occlusion. In this table, the postoperative results are based on objective data comparing pre- and postoperative studies. If postoperative studies are unavailable, the result is described as "too recent" even though the clinical course suggests a successful result.

This technique, we believe, is particularly adaptable for operations on the pulmonary valve and on the outflow tract of the right ventricle. A very deliberate careful plastic operation on the deformed valve can easily be performed in from 3 to 5 minutes of circulatory arrest. The danger of coronary air embolism is almost nil in view of the position of the patient, in table III, the operations on pulmonary

TABLE II

DIRECT VISION INTRA-CARDIAC PROCEDURES WITH CIRCULATORY ARREST

(81 patients, 84 procedures)

	I. Pure (single) defects				
Disease	Patients	Total cure	Partial cure	Too recent	Died
Pulmonary valvular stenosis	22	11	1	10	0
Pulmonary infundibular stenosis	2	1	1	0	0
Auricular septal defect (secundum)	29	21	0	5	3
Auricular septal defect (primum)	4	0	1	1	2
Ventricular septal defect	5	0	1	0	4
	62	33	4	16	9
	II. Combined (multiple) defects				
Disease	Patients	Total cure	Partial cure	Too recent	Died
Tetralogy of Fallot:					
A. Valvular stenosis	6	0	6	0	0
B. Infundibular stenosis	7	0	5	0	2
Auricular septal defect:					
A. Pulmonary stenosis (trilogy)	5	1	1	1	2
B. Ventricular septal defect	1	0	0	0	1
	19	1	12	1	5

TABLE III

OPERATIONS FOR PULMONARY STENOSIS

Disease	Patients	Total cure	Partial cure	Too recent	Died
Isolated valvular stenosis	22	11	1	10	0
Isolated infundibular stenosis	2	1	1	0	0
Valvular stenosis with tetralogy	6	0	6	0	0
Infundibular stenosis with tetralogy	7	0	5	0	2
Trilogy of Fallot	4	1	1	1	1
	41	13	14	11	3

valve and infundibulum are recapitulated. As is apparent, the only death following valvular operation occurred in a patient in whom there was an associated large atrial septal defect, the so-called Trilogy of Fallot. This infant died of some form of circulatory failure 16 hours following operation. This anomaly poses special problems and we are still uncertain whether one should repair the septal defect or the valve first, or should one attempt both at the same sitting. For resection of infundibular stenosis, one must be careful not to resect too much. In one patient, with Tetralogy, for example, following infundibular resection, a large aneurysmal dilatation of the thin-walled *infundibular chamber* occurred. Subsequent attempt to repair this complication was fatal. The other death occurred as a result of staphylococcic septicemia following a two week period of anuria. This patient underwent ventricular fibrillation during surgery, and a period of hypotension presumably occurred during resuscitation. This is the only death in this entire group in which hypothermia itself was considered to be contributory.

Atrial septal defect (table IV) is also well-managed by direct vision suture, using cooling to allow circulatory arrest. Particularly satisfactory are those patients with the so-called secundum-type lesion. A continuous suture is extremely effective in obtaining complete closure of these lesions, while aberrant pulmonary veins can be easily positioned to the left of the closure, except those which enter into the superior vena cava itself. Primum-type lesions or atrio-ventricularis communis are more difficult technically to manage within the allotted time limit. One of the deaths resulted from hemorrhage immediately postoperatively following attempt to repair atrial septal defect after conclusion of pulmonary valvuloplasty in a patient with Trilogy. As mentioned previously, three deaths were associated with thromboembolism, presumably of the pulmonary vascular tree, either arterial or venous. We believe for adults, therefore, that anti-coagulants should be given for a period of two weeks following repair of atrial septal defect. The other death occurred on the artificial kidney 12 days postoperatively, the anuria presumably due to transfusion reaction.

Ventricular septal defect, on the other hand, is a lesion of sufficient complexity anatomically to render the technical repair too difficult to accomplish safely within the current eight minute time limitation. As can be seen, only one of five patients survived such attempts. Two others had successful closure, but died a circulatory death within a few hours postoperatively. The other two were technical failures. This experience led us to abandon this procedure until longer periods for open operation became safely available, either by use of extra-corporeal circulations, or by better application of hypothermia.

TABLE IV

OPERATIONS FOR ATRIAL SEPTAL DEFECT

Disease	Patients	Total cure	Partial cure	Too recent	Died
Auricular septal defect (secundum)	30	21	0	5	4
Auricular septal defect (primum)	4	0	1	1	2
Trilogy	2	1	0	0	1
	36	22	1	6	7

Summary. 1. Experience with 105 patients undergoing cardiac surgery during hypothermia has been described and discussed. Of these, 81 had direct-vision open-heart operations during circulatory arrest.

2. As currently applied in our hands, the safe parameters for open-heart operations appear to be a right heart cardiotomy, hypothermia not deeper than 26° C., and circulatory occlusion not to exceed eight minutes.

3. The chief causes of death have been ventricular fibrillation, post-operative hemorrhage, and delayed thrombo-embolic phenomenon. The methods currently being adopted to overcome these difficulties are discussed.

4. For cyanotic patients and those with severe tachycardia, cooling appears to improve operative risk when standard closed operations are performed.

5. Pulmonary valvular and infundibular stenosis, and atrial septal defect, especially of the secundum variety, are effectively treated at low risk by direct-vision repair. At the present time, we consider this method the treatment of choice for these lesions.

DISCUSSION

Dr. F. J. Lewis: Those of us who use hypothermia in Minnesota have used a slightly different technique. Although we strive to avoid respiratory alkalosis and Dr. Swan to produce it, there is some similarity, of course, because we both attempt to maintain a constant pH level. That may be more important than anything else in the technique. Except for that difference, most of our experience has agreed with Dr. Swan's, and I think that hypothermia provides, mechanically, the simplest method at the present time for doing open heart surgery. It provides the driest operative field for this type of operation, and it provides the best way at the present time, certainly, for doing open operations on adults where with heart-lung machines and other techniques the problem is quite a bit more complicated than it is in infants. In our own series of cases we have operated with success on adult patients as old as 61.

As to what operations you can do with hypothermia, I think that problem is obviously still unsettled. With a careful exploration of the heart with the finger before the open cardiotomy, and a carefully rehearsed technique, a great deal can be accomplished in seven minutes or less. For example, we recently operated on a patient with total anomalous pulmonary venous drainage; all the pulmonary veins ended in the right atrium. To repair this we made a large atrial septal defect and reconstructed the right atrium. The operation took eight minutes. Apparently the results have been completely successful. Further examples can be given. Recently we also operated on a tri-atrial heart under direct vision during hypothermia, and that operation took but three and one-half minutes. Our average time for the atrial septal defects has been four and one-half minutes. The high defects have taken us the longest to repair.

Dr. Jerome H. Kay: In order to prolong the time during which we can work inside the right ventricle, Doctors Robert Gaertner, James Isaacs, Richard Dever, and I have perfused the head and heart in a group of 157 animals.

In all of these animals the right ventricle was open for 15 to 30 minutes. We collected arterial blood from the femoral artery of donors and added 40 milligrams

of heparin to each liter of blood. The blood was perfused from an ordinary 2 liter graduated cylinder with the use of a sigma pump.

The technique employed consists of cooling these animals to a rectal temperature of 32 to 34° C. The right brachial (subclavian) artery is temporarily occluded distal to the internal mammary artery. A catheter is inserted into the internal mammary artery in order to take pressures during the period of bypass. A systolic pressure of 80 to 120 millimeters of mercury is maintained during the period of bypass.

The left brachial (subclavian) artery is occluded temporarily. The superior cava is occluded around a catheter that has been inserted through the azygos vein. Blood is drained from the superior vena cava by gravity. The inferior vena cava is occluded and the aorta cross-clamped distal to the origin of the left brachial artery. The sigma pump is turned on and blood is perfused in a proximal direction into the right common carotid artery. The blood, therefore, is pumped into the arch of the aorta. It can only perfuse the heart through the coronary arteries and the brain and head through the left common carotid artery.

We have used the right subclavian artery for the site of perfusion instead of the carotid artery in some dogs, and the results have been the same.

The last 20 dogs were cooled to a rectal temperature of 32 to 34° C. and the right ventricle was open for 15 to 30 minutes. The aorta was cross-clamped for 30 to 37 minutes.

In these dogs none of the 20 hearts fibrillated. Seventeen of twenty dogs are long-term survivors. The other three dogs died within the first 48 hours postoperatively. Gross and microscopic studies revealed pulmonary congestion.

The method described is safe and allows open heart surgery in the dog for periods of time up to 30 minutes.

During the past year Dr. Robert Gaertner and I have used hypothermia in more than 250 dogs in order to perform intracardiac procedures. All of these animals had inflow occlusion. Early in our experiments we cooled the dogs to a final rectal temperature of 20 to 25° C. and maintained inflow occlusion for 10 to 12 minutes. It soon became evident, however, that with inflow occlusion for longer than 7 or 8 minutes, the mortality rate was extremely high. We also noted that the incidence of ventricular fibrillation was very high at temperatures lower than 30° C. Temperatures of 30 to 32° C. safely protected the brain against damage for periods of inflow occlusion of 8 minutes. The incidence of fibrillation with inflow occlusion for 8 minutes at 30 to 32° C. was low and the recovery rate high. We therefore recommend that procedures requiring inflow occlusion be performed at 30 to 32° C. and that these procedures require less than 8 minutes.

Dr. I. K. R. McMillan: Two or three years ago we noticed something which at the time was regarded as ridiculous, namely, that we lost a lot more dogs from ventricular fibrillation in the summer than in the winter. This was in England, but Dr. Swan has had the same experience, and it was also reported by Cookson about five years ago. It has occurred sufficiently often in our experience that I think it is a matter that needs investigating. It is one of the interesting side issues of hypothermia which is little discussed, and perhaps my comment may stimulate others to add their observations.

Dr. William P. Longmire, Jr.: We have recently reviewed 100 cases in which

various degrees of hypothermia were utilized, and have classified these cases in three different groups.

The first group was called "The Controlled Temperature Group." In cases from this group, the temperature ranged from 34° C. to 30° C. The second group, in which temperatures ranged from 30° to 25° C., was called "The Moderate Hypothermia Group." The third group, which was labelled the "Deep Hypothermia Group," included those cases in which temperatures went below 25° C.

Most of these cases did not involve an interruption of the blood flow through the heart. They were, for the most part, closed cardiac procedures, and hypothermia was utilized because of the severe nature or character of the disease process.

We attempted to analyze these cases with regard to the ill effects of hypothermia alone. This was exceedingly difficult to do, particularly with respect to the cases in the deep hypothermia group, since many of these patients had conditions which were essentially incompatible with life.

Of the 10 cases in the deep hypothermia group, only three cases survived the immediate postoperative period, and there was only one long-term survivor.

There were two patients who exhibited severe postoperative bleeding which might possibly have been correlated with the degree of hypothermia. One of these patients was re-explored and found to have multiple areas of bleeding for which little could be accomplished. The other patient was treated merely by repeated aspirations, and subsequently survived the procedure. Similar problems have been encountered in cases of this type without the use of hypothermia.

Our only conclusion was that in this series of 100 cases there was no death clearly attributable to the use of hypothermia alone; nor were there any complications that might not have occurred had the hypothermia not been used.

Dr. Jean Cahn: I think that in operations on the bloodless heart there is a problem if the duration of the arrest of the circulation is over 20 minutes. We have two possibilities: (1) to infuse oxygenated blood into the occluded aorta so as to prolong the circulation into the coronary system; or (2) to be not inhibited by this problem and to consider that it is possible to operate on the bloodless heart for a period of 25 minutes without any blood supply into the coronary system. In fact, that is possible; but yesterday, when I told you that it was possible to arrest the blood circulation for 25 minutes without any ventricular fibrillation because of sino-atrial blockade, I gave you only 50 per cent of the problem and of the solution.

To resuscitate the heart after 25 minutes of arrest of the circulation, we must inject into the right chamber before the release of the caval clamping a mixture of A.T.P. and cytochrome-C. Under those conditions it is possible to re-establish the normal beat of the heart after only 30 seconds to one minute of cardiac massage. The cardiac massage must be done carefully. We have only to push out of the right cavity the blood and the mixture of A.T.P. and cytochrome-C.

Lt. Col. Carl W. Hughes, MC, USA: In keeping with the constant concern with ventricular fibrillation in the hypothermic animal, it was interesting to note in the film by Drs. Andjus, Smith, and Lovelock that in the supercooled animal, consideration was given to rewarming the heart faster than the rest of the body. At the Walter Reed Army Institute of Research, in a study of the tolerance of the hypothermic normal dog's heart to ventricular fibrillation, adult dogs were cooled until spontaneous ventricular fibrillation occurred. The animals were allowed to

fibrillate for various periods of time. These dogs were found to survive 60 minutes of ventricular fibrillation with complete recovery. After 75 and 90 minutes of fibrillation, survivors were found to have only a mild, persistent hindquarter weakness. Resuscitation in these animals was not a problem, but as the periods of ventricular fibrillation were lengthened to three, four, and five hours, resuscitation became increasingly difficult.

Resuscitation was accomplished by removing the animal from the ice water bath, placing the animal on a warm water mattress, opening the chest and irrigating of the pleural spaces with sterile saline at 45° C. With each 1° C. rise in rectal temperature a single defibrillation shock of 200 volts was administered to the heart for a period of 0.13 second. This routine was continued until defibrillation occurred and the animal had established its own adequate circulation. This warm saline irrigation, which we considered an extremely important factor in converting the fibrillating heart, was continued about the heart until a rectal temperature of 28° C. was reached.

Dr. Swan: I agree with Dr. Longmire that it is difficult to evaluate clinically what happens when one is dealing with a very sick patient and the patient dies. To try to implicate any part of the procedure is almost impossible. I hope that many others as well will think about and attempt to evaluate this problem.

I would like to thank Dr. McMillan for his comment, because in our laboratory, at least, we have found that the time of the year has a profound effect upon our experimental results. We in Denver have hot summers and fairly cold winters. We do not have the advantages of having an air-conditioned, temperature-controlled animal room, and our dogs are subjected in the wintertime to cold nights.

I believe this concept of pre-conditioning is of considerable importance in experimental hypothermia, and that it is one of the major causes why there is a great variety of results obtained in different parts of the country in studying this problem.